Lophomonas blattarum Infection or Just the Movement of Ciliated Epithelial Cells?

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Introduction

Lophomonas blattarum (*L. blattarum*) is a multiflagellated protozoan, which parasitizes in the intestinal tracts of termites and cockroaches, belonging to the *Lophomonas* suborder, *Hypermastigida* order. More than 100 cases of bronchopulmonary *L. blattarum* infection have been reported since 1993. However, we identified the movable cells from the bronchoalveolar lavage fluid (BALF) of six patients with pulmonary diseases under an electron microscope, and eventually found that these cells were actually bronchial ciliated epithelial cells, which were basically identical with reported *L. blattarum* in morphology under light microscope in the literature.[1] Through careful literature review, we found that all of the reported *L. blattarum* infections were just diagnosed by morphology under light microscope rather than electron microscope, isolation and culture, or molecular procedures; images exhibited in these literatures were all compatible with the microscopic characteristics of bronchial ciliated epithelial cells. There was no robust evidence to consider *L. blattarum* as a pathogen of respiratory infection so far. Therefore, we believed that bronchopulmonary *L. blattarum* infection was probably misdiagnosed. Here, we summarized the insufficient evidences about current *L. blattarum* infection and its difference with ciliated epithelial cells, to enhance the discrimination capability in clinical activities and avoid misdiagnosis in future.

Clinical Characteristics of "*Lophomonas blattarum*" Infection

L. blattarum infection in human was first described by Chen and Meng in 1993.[2] We used "*L. blattarum*" and "*Hypermastigote*" as keywords to search relevant literature from Wanfang Data, China National Knowledge Infrastructure, and PubMed. Getting rid of duplicate cases, a total of 43 literatures were enrolled, of which 35 literatures were written in Chinese, seven in English, and one in Spanish.[2-44] One hundred and fifty-four cases were suffered from *L. blattarum* infection, including 149 cases of bronchopulmonary infection, three of sinus infection, one of urinary infection, and one of intrauterine infection. A majority of the bronchopulmonary infection cases were reported in China (141/149, 94.6%), in addition to six cases in Peru and two cases in Spain. The components of diagnosis were pneumonia (79/149, 53.0%), chronic obstructive pulmonary disease (22/149, 14.8%), lung cancer (3/149, 2.0%), allergic bronchopulmonary aspergillosis (1/149, 0.7%), interstitial lung disease (4/149, 2.7%), lung abscess (8/149, 5.4%), tuberculosis (17/149, 11.4%), chronic cough (5/149, 3.4%), pulmonary cyst (1/149, 0.7%), eosinophilia (2/149, 1.3%), asthma (5/149, 3.4%), atelectasis (1/149, 0.7%), and bronchiectasis (1/149, 0.7%). *L. blattarum* was considered as an opportunistic infection, for which 31 cases were reported to be immunosuppressive hosts, including 24 patients with kidney allograft transplantation, two with long-term corticosteroid treatment, two with chemotherapy of cytotoxic drugs, one with hepatic transplantation, one with allogeneic hematopoietic stem cell transplantation, and one with HIV infection. Most cases were not under immunosuppressive

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status although diseases such as tuberculosis could impact immune responses. Thirty-two cases (21.5%) had eosinophilia, 82 cases (55.0%) had normal eosinophil counts, and the remaining lacked the information about eosinophil counts. The majority of patients received treatment of metronidazole, tinidazole, or ornidazole. One case received quinacrine following treatment failure of metronidazole.[2]

The source of specimens came from sputum (95/149, 63.8%), BALF (81/149, 54.4%), bronchoscopic brushing smear (4/149, 2.7%), endotracheal aspirates (3/149, 2.0%), throat swab (1/149, 0.7%), and cystic fluid in pulmonary cyst (1/149, 0.7%). Among the 37 literatures of bronchopulmonary infection, all of the so-called *L. blattarum* were identified by the use of light microscope, and microscope images were provided in 22 literatures. However, our investigation revealed that the light microscopic structures of all the published images were not adequate to prove them as *L. blattarum*; in contrast, some showed obvious features belonging to ciliated epithelial cells. Martinez-Girón *et al.* also doubted some literatures misjudging ciliated epithelial cells for *L. blattarum*.[31,45,46] The same skeptical issue was once raised by authors in China.[47]

Fine Structures Under Microscope

Lophomonas comprises two species, including *Lophomonas striata* (*L. striata*) and *L. blattarum*. *L. striata* was first identified from the gut of the cockroach *Blatta orientalis* by S. Stein in 1860.[48] The structure of *L. blattarum* was identified by light microscope in 1911, transmission electron microscope in 1961, and scanning electron microscope in 1990.[49] The shape of *L. blattarum* is usually round, oval, or pyriform, with size range from approximately 15 to 40 μm, with a tuft of flagella extending from the anterior end of the organism. Phagocytic vacuoles can be found in the cytoplasm. Ciliated epithelial cells are conical or columnar in shape, provided with a tuft of kinocilia at their apical cell face, rhythmically moving outward to eliminate excretions and trapped foreign materials.

The discrimination of *L. blattarum* and ciliated epithelial cells under light microscope is usually subtle. Nevertheless, there are some morphological differences to help judgment. The first is the recognition of flagella and cilia through their length and orientation, which belonged to *L. blattarum* and ciliated epithelial cells, respectively. The flagella tuft of *L. blattarum* is composed of 50 or more flagella, with unequal length range from 5 to 10 μm, the longer ones locating in the center of the tuft while shorter ones in the periphery. The cilia tuft of ciliated epithelial cells is composed of approximately 200 cilia, with nearly identical length of 7–8 μm. Under light microscope, the flagella are irregularly arranged while the cilia are regularly oriented. Second, the relative position of the nucleus and flagella or cilia tuft is totally different. The nucleus of *L. blattarum* is located at the base of the flagella tuft, both at the anterior end of the cell. Whereas nuclei of the ciliated epithelial cells located at the bottom of the cell, opposite to the cilia tuft, which emerges from the apical face of the cell. Third, the axial filament could be found at the posterior end of *L. blattarum*, but absolutely not in ciliated epithelial cells.

Electron microscopy provides ultrastructure of *L. blattarum* and definites difference from ciliated epithelial cells. Calyx, axial filament, and perinuclear tubules are special structures of *L. blattarum*.[50] These structures may be exhibited obscurely by light microscopy while the detailed ultrastructure can only be revealed by electron microscopy. The funnel-shaped calyx restricts the nucleus in the anterior area, nearby the flagella, in accordance with the light microscopic feature. Lamellar structures of the calyx gather posterior to the nucleus to form axial filament, prolonging to the base extremity of the organism. Perinuclear tubules radiate from the nucleus, dividing into proximal tubules covered with ribosomes and distal tubules without ribosomes, functioning equivalent to the rough- and smooth-surfaced endoplasmic reticulum, respectively.[50] In our research, we did not find the ultrastructure above in the cells mimicking *L. blattarum* from BALF, which was finally identified as ciliated epithelial cells.[1]

Does *Lophomonas blattarum* Infection Really Exist?

Combined with the morphological features mentioned above, we thought that the diagnosis of bronchopulmonary *L. blattarum* infection was unsubstantiated. There seems to be a few supporting clinical evidence for *L. blattarum* infection in the reported literatures so far, yet each has another explanation. First of all, there was large heterogeneity of the treatment. Some literatures reported the failure of initial antibiotic treatment, and the condition improved after metronidazole treatment. However, there were failures of metronidazole treatment as well.[2,24] The improvement could not be simply attributed to the anti-protozoa effect of metronidazole; instead, it has excellent anti-anaerobe property, which could improve therapeutic efficacy in patients with aspiration pneumonia and lung abscess. Other antimicrobial administration could tangle our judgment on therapeutic response. For instance, patients complicated with bacterial infections almost always received other antibiotics, and patients complicated with tuberculosis received anti-tuberculosis agents at the same time, which played a predominant role in the therapeutic response. Therefore, the response to metronidazole could not be treated as a convinced supplemental proof of *L. blattarum* infection. Second, some cases had epidemiological history of cockroach exposure, which brought in the hypothesis that *L. blattarum* might infect human beings by inhalation aerosol containing *L. blattarum* cysts when they were excreted into the environment by cockroaches, or through contaminated food or clothes.[12,17,26] Whereas *L. blattarum* was not found by dissecting sixty cockroaches in patients' living environment.[17] Likewise, we dissected more than fifty cockroaches without any positive findings.[1] Third, the light microscopic structure is not reliable without the confirmation of electron microscopy,

even if suspicious structure of axial filament was described in some literatures. Dead bodies of the "protozoa" detected after therapy was not showed in images as well.[23] Repeated sputum or BALF smears revealed disappearance of the so-called *L. blattarum* according to some literatures, and we thought it was probably due to the randomness for the detection of ciliated epithelial cells. On the other hand, the mobile cells could still be detected after treatment in some cases.[13] The mobility was described as a distinguishing feature, yet we found that ciliated epithelial cells could show similar movement after detached from airway epithelium for a long period [Supplementary Videos 1 and 2]. Moreover, we found the majority of reported *L. blattarum* pictures shown in literatures are of very similar or identical traits in morphology with ciliated epithelial cells presented by our group.[1] Finally, most cases were reported in China, hardly seen in other regions of the world; however, there was no evidence that *L. blattarum* infection was an endemic disease that means misdiagnosis is more likely.

In conclusion, bronchopulmonary *L. blattarum* infection is still an unconvinced mystery, with inconclusive clinical features, route of transmission and pathogenesis, since it is difficult to be distinguished from normal bronchial ciliated epithelial cells only via light microscopy. Previous literatures might misidentify it for the last two decades. Supporters should provide either detailed ultrastructure by electron microscopy or molecular evidence by isolation and culture to validate whether *L. blattarum* infection really exists or not. Clinicians need to be more cautious to make the diagnosis before obtaining tangible proofs in clinical practice.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

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Conflicts of interest

There are no conflicts of interest.

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